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Ventilator-induced respiratory muscle weakness

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Abstract

Clinicians have long been aware that substantial lung injury results when mechanical ventilation imposes too much stress on the pulmonary parenchyma. Evidence is accruing that substantial injury may also result when the ventilator imposes too little stress on the respiratory muscles. Through adjustment of ventilator settings and administration of pharmacotherapy it is possible to render the respiratory muscles almost (or completely) inactive. Research in animals has shown that diaphragmatic inactivity produces severe injury and atrophy of muscle fibers. Human data have recently revealed that 18 to 69 hours of complete diaphragmatic inactivity associated with mechanical ventilation decreased the cross-sectional areas of diaphragmatic fibers by half or more. The atrophic injury appears to result from increased oxidative stress leading to activation of protein-degradation pathways. Scientific understanding of ventilator-induced respiratory muscle injury has not reached the stage where it is possible to undertake meaningful controlled trials and thus it is not possible to render concrete recommendations for patient management. In the meantime, clinicians are advised to select ventilator settings that avoid both excessive patient effort and also excessive respiratory muscle rest. The contour of the airway pressure waveform on a ventilator screen provides the most practical indication of patient effort, and clinicians are advised to pay close attention to the waveform as they titrate ventilator settings. Research on ventilator-induced respiratory muscle injury is in its infancy and portends to be an exciting area to follow.

The most common reason to institute mechanical ventilation is to decrease patient distress resulting from an increase in work of breathing (1). In this situation, the ventilator is functioning as an additional set of muscles, and so decreases the load placed on the patient's own respiratory muscles. The second major indication for mechanical ventilation is to improve oxygenation, as, for example, in patients with the acute respiratory distress syndrome (ARDS) (1). A ventilator improves oxygenation by increasing tidal volume and end-expiratory lung volume, and by better matching of ventilation and perfusion within the lung parenchyma (2). While the oxygen-enhancing action of the ventilator is not directed at the respiratory muscles per se, patients with impaired oxygenation are commonly treated with antibiotics (3), corticosteroids (4), sedatives (5) and neuromuscular agents (6), all of which can weaken respiratory muscles.

Every patient who survives an episode of acute respiratory failure faces a major challenge at the point of ventilator discontinuation. The main reason that patients fail weaning attempts is because their work of breathing is high consequent to abnormal lung mechanics (increased resistance, decreased compliance) and their respiratory muscles are unable to cope with the increased load (7). From the above account, it is evident that performance of the respiratory

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muscles is a dominant consideration at the points when mechanical ventilation is first instituted and when it is being withdrawn.

A major concern of critical care physicians is the growing awareness that mechanical ventilation can harm the lung. From the earliest days of intensive care, it has been recognized that use of high airway pressure can rupture the lung parenchyma, causing a pneumothorax. In 1974, Webb and Tierney demonstrated that mechanical ventilation can cause hemorrhagic and edematous lesions independent of barotrauma (8). This seminal observation was extended by other animal experiments and the alveolar injury has been shown to result from the use of high tidal volumes; the injury has been named volutrauma or ventilator-induced lung injury (9). Studies in animals were followed by studies in patients, which culminated in randomized controlled trials that have shown that use of high tidal volume leads to increased mortality in patients with ARDS.

Just as mechanical ventilation can damage the lung parenchyma, investigators have postulated that the ventilator can damage the respiratory muscles (10). The fear is that mechanical ventilation lowers demands on a patient's respiratory muscles to such an extent that they become inactive, resulting in injury and atrophy at a structural level. In contrast to research on ventilator-induced lung injury, scientific understanding of ventilator-induced respiratory muscle injury has not reached the stage where it is possible to undertake meaningful randomized controlled trials and thus it is not possible to render concrete recommendations for patient management. Nevertheless, the accruing biological and pathophysiological research on the effect of mechanical ventilation on the respiratory muscles is leading many experts to change their approach to ventilator management.

Animal models of ventilator-induced muscle injury

During the past two decades, several groups have studied the effect of mechanical ventilation on the muscles of laboratory animals. A seminal study showed that 11 days of controlled mechanical ventilation produced a 46% decrease in respiratory muscle strength (11). In that study, animals received neuromuscular blocking agents to ensure that they made no respiratory efforts; controlled mechanical ventilation differs from the more commonly employed mode, assist-control ventilation, where patients continue to make some respiratory efforts in addition to receiving assistance from the ventilator (12). Subsequent studies have revealed that complete cessation of diaphragmatic activity with controlled mechanical ventilation – alone (13) or in combination with neuromuscular blocking agents (14) – results in injury and atrophy of diaphragmatic fibers. Muscle fibers generate less force in response to stimulation, not simply because of their decreased bulk but even when normalized for cross-sectional area. The decrease in diaphragmatic force ranges from 20% to more than 50%. The alterations in muscle function occur rapidly, within 12 hours of instituting mechanical ventilation (15), and they appear to increase as ventilator duration is prolonged (16).

Increasing experimental evidence suggests that oxidative stress is the most proximal mechanism in the biochemical cascade that leads to ventilator-induced muscle injury (17;18). Oxidative stress decreases contractility by causing protein oxidation and by promoting protein catabolism (18). Other mechanisms that contribute to muscle-protein loss include apoptosis (15) and decreased protein synthesis (19).

The degree of injury in animal studies depends on how the ventilator is set. Sassoon et al (20) have shown that maintenance of some respiratory muscle activity, through the employment of assist-control ventilation, appeared to prevent the impairment in diaphragmatic contractility, whereas completely controlled ventilation induced a 48%

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decrease in contractility. Intermittent bursts of unassisted breathing during a course of controlled ventilation have also been shown to limit injury (21).

In animal models, limb immobilization (with a cast) in a shortened position accelerates protein degradation and causes myonuclear apoptosis (22). Whether the application of PEEP (and thus shortening of the diaphragm) during controlled mechanical ventilation further aggravates the structural injury caused by muscle disuse remains to be determined.

Evidence for ventilator-induced muscle injury in patients

Levine et al (23) have recently presented human data that support the findings of the animal studies. They obtained biopsies of the costal diaphragms from 14 brain-dead organ donors. These patients exhibited diaphragmatic inactivity and had received mechanical ventilation for 18 to 69 hours. They also obtained intraoperative biopsies of the diaphragms of 8 patients undergoing thoracic surgery for suspected lung cancer; these control patients had experienced diaphragmatic inactivity and mechanical ventilation for 2 to 3hours.

Histologic measurements revealed marked diaphragmatic atrophy in the brain-dead patients. Compared with the control group, the mean cross-sectional areas of muscle fibers were significantly decreased by more than 50%. The cross-sectional area of fibers of the pectoralis major, a muscle not affected by mechanical ventilation, was equivalent in the two groups. This finding indicates that the diaphragmatic atrophy experienced by the brain-dead patients was not part of some generalized muscle-wasting disorder.

Biochemical and gene-expressionstudies suggest that the atrophy resulted from oxidative stress leading to muscle protein degradation. Evidence of oxidative stress is indicated by a 23% lower concentration of glutathione in the diaphragms of brain-dead patients than in the control (23). Evidence of enhanced muscle protein degradation is indicated by a 154% greater expression of active caspase-3 in the brain-dead patients than in the controls (23). Caspase is an enzyme that can dissociate proteins from the myofibrillar lattice, a critical step in muscleproteolysis.

Muscle proteolysis typically involves the ubiquitin–proteasome pathway, a cytosolic ATP-dependent protease system (24). In this system, proteins catabolized by the proteasome are first “tagged” with a small chain of ubiquitin molecules. Tagging with ubiquitin is an ATP-requiring process that involves specific “ubiquitin ligases” such as atrogin-1 and muscle ring finger-1 (MuRF-1) (24). In the study of Levine et al (23), the number of messenger RNA transcripts for atrogin-1 and MuRF-1 were 200% and 590% higher, respectively, in the brain-dead patients than in the controls.

Based on these findings, Levine et al (23) concluded that 18 to 69 hours of complete diaphragmatic inactivity and mechanical ventilation produced marked diaphragmatic atrophy as a result of increased oxidative stress leading to activation of protein degradation pathways.

Other human data support the likelihood that mechanical ventilation can induce respiratory muscle atrophy. Knisely et al (25) performed autopsies in 13 infants who died after receiving mechanical ventilation for ≥12 days and 26 infants who died after ventilation for ≤7 days. The cross-sectional areas of diaphragmatic fibers were much smaller in the infants who received the longer duration of mechanical ventilation. Fibers taken from strap and tongue muscles were similar in the two groups. Ayas et al (26) reported a patient with a high spinal-cord injury whose diaphragmatic pacemaker failed to function on the left side. Ultrasonography performed after eight months of mechanical ventilation revealed atrophy of

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the left hemidiaphragm. Pacemaker stimulation of the right phrenic nerve for 30 minutes a day was sufficient to prevent atrophy of the right hemidiaphragm.

Over the past two decades, research on respiratory muscle function in ventilated patients has focused mostly on patients at the time of weaning. The pressure generated by a patient during a maximal inspiratory pressure ($P_I$max) maneuver is taken as a measure of respiratory muscle strength. Numerous studies have shown that $P_I$max values do not discriminate between weaning-success and weaning-failure patients. These findings led to the belief that respiratory muscle weakness was not a determinant of clinical outcome in ventilated patients. Recent studies have revealed that $P_I$max can misrepresent respiratory muscle strength because the values are heavily influenced by patient motivation and cooperation (24). A more objective measure of diaphragmatic strength is obtained by stimulation of the phrenic nerves and recording the resulting transdiaphragmatic pressure (Figure 1). In healthy subjects, twitch transdiaphragmatic pressures is 35±8 (SD) cm H_2O (27). Ambulatory patients with respiratory muscle weakness secondary to chronic obstructive pulmonary disease have twitch transdiaphragmatic pressures of 20±7 (SD) cm H_2O (28). Patients requiring mechanical ventilation have much lower twitch pressures, many below 15 cm H_2O (29;30). These observations indicate that diaphragmatic weakness in ventilated patients is much greater than previously suspected, and raises the possibility that the diaphragmatic atrophy described by Levine et al (23) may be not uncommon. Measurement of twitch pressure has not been evaluated in terms of its reliability as a predictor of weaning outcome and, given the considerable skill required to make the measurement, it is doubtful that it will ever become a part of everyday clinical practice.

Physicians should not assume that respiratory muscle weakness in a ventilated patient is diagnostic of ventilator-induced muscle injury. While ventilator injury is one possibility, numerous other common conditions, including sepsis (24) and the administration of antibiotics (3), corticosteroids (4), sedatives (5) and neuromuscular agents (6), can also induce respiratory muscle weakness (Table 1).

Implication for setting the ventilator

Research on ventilator-induced muscle injury is about twenty years behind research on ventilator-induced lung injury (9;10). The evidence to date, nevertheless, carries several implications for clinical management. The use of controlled mechanical ventilation and neuromuscular blocking are generally avoided unless a patient continues to fight the ventilator despite all attempts to identify and reverse the cause (2). Animal data suggest that use of assisted-ventilator modes, where a patient makes some respiratory effort during every ventilator breath, may attenuate the development of diaphragmatic injury (20). Data on this point, however, are very limited. It remains possible that large reductions in patient effort, short of complete inactivity, may be sufficient to induce muscle injury – although less than that caused by controlled ventilation. The amount of work that a patient performs while a ventilator is delivering a breath depends largely on a patient's respiratory center drive at the point of triggering the ventilator (r=0.78) (31) (Figure 2). Sedative and analgesics agents, widely used in ventilated patients, markedly decrease respiratory drive; by decreasing patient work during assisted breaths, these agents may contribute to ventilator-induced muscle injury.

Pressure-time product is the amount of pressure generated by the respiratory muscles during inspiration and it is commonly used to quantify respiratory effort in research studies. The average value in a healthy person is about 90 cm H_2O/sec/min (7). For patients in the throes of acute respiratory failure (before receiving mechanical ventilation), the average pressure-time product is about 400 cm H_2O/sec/min (7). Although pressure-time product is not part of

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routine clinical practice, it provides a mental framework when selecting ventilator settings. At the time a patient is commenced on mechanical ventilation, ventilator settings are generally adjusted and sedation is titrated to substantially decrease patient effort (aiming for a pressure-time product of about 70 to 110 cm H_2O/sec/min). We worry that too great a reduction in patient effort (such as below a pressure-time product of 40 cm H_2O/sec/min) might result in the development of ventilator-induced muscle injury. We emphasize that our caution is based on circumstantial evidence and that the appropriate tradeoff between increased patient effort and excessive respiratory muscle rest is unknown. Definitive data on patient outcome are not expected for many years.

In everyday practice, the best indicator of patient effort during mechanical ventilation is the contour of the airway pressure waveform on the ventilator screen (32–34). Figure 3 shows the typical waveform in a patient soon after institution of mechanical ventilation, while the patient is still experiencing severe respiratory distress, the waveform produced by controlled mechanical ventilation where the patient is making no respiratory effort, and the waveform in a patient receiving an appropriate level of ventilator assistance. Ventilator settings need to be adjusted to navigate a course between the excessive patient effort (as depicted in the left panel of Figure 3) and excessive respiratory muscle rest (as depicted in the middle panel). The human data collected by Levine et al (23) together with the animal data demonstrating ventilator-induced muscle injury (10) provide an added impetus to paying close attention to pressure waveforms. Although biologically plausible, the effect of waveform monitoring on patient outcome has not been tested.

It is possible that novel therapies may prove beneficial in preventing or reversing this injury. For example, a protease inhibitor, leupeptin, was recently shown to completely prevent atrophy of diaphragmatic fibers after 24 hours of controlled ventilation in rats (35). Administration of leupeptin abolished the increased activity of two intracellular proteases calpain and cathepsin B induced by controlled mechanical ventilation (35). Likewise, the antioxidant Trolox has been shown to retard proteolysis and prevent diaphragmatic contractile impairment in animals receiving controlled mechanical ventilation (36). Trials of such agents have not been undertaken in ventilated patients.

In conclusion, clinicians have long been aware that substantial lung injury results when a ventilator places too much stress on the pulmonary parenchyma. For more than twenty years, clinicians have known that patients can perform excessive respiratory muscle work while receiving mechanical ventilation if the mode and settings are not carefully selected. Increasing evidence now suggests that too little stress on the respiratory muscles may cause disuse atrophy and muscle damage. To navigate a patient's safe passage between the Scylla and Charybdis of excessive patient effort and excessive respiratory muscle rest, we suggest that clinicians carefully titrate ventilator settings and pay close attention to the contour of the airway pressure waveform.

Acknowledgments

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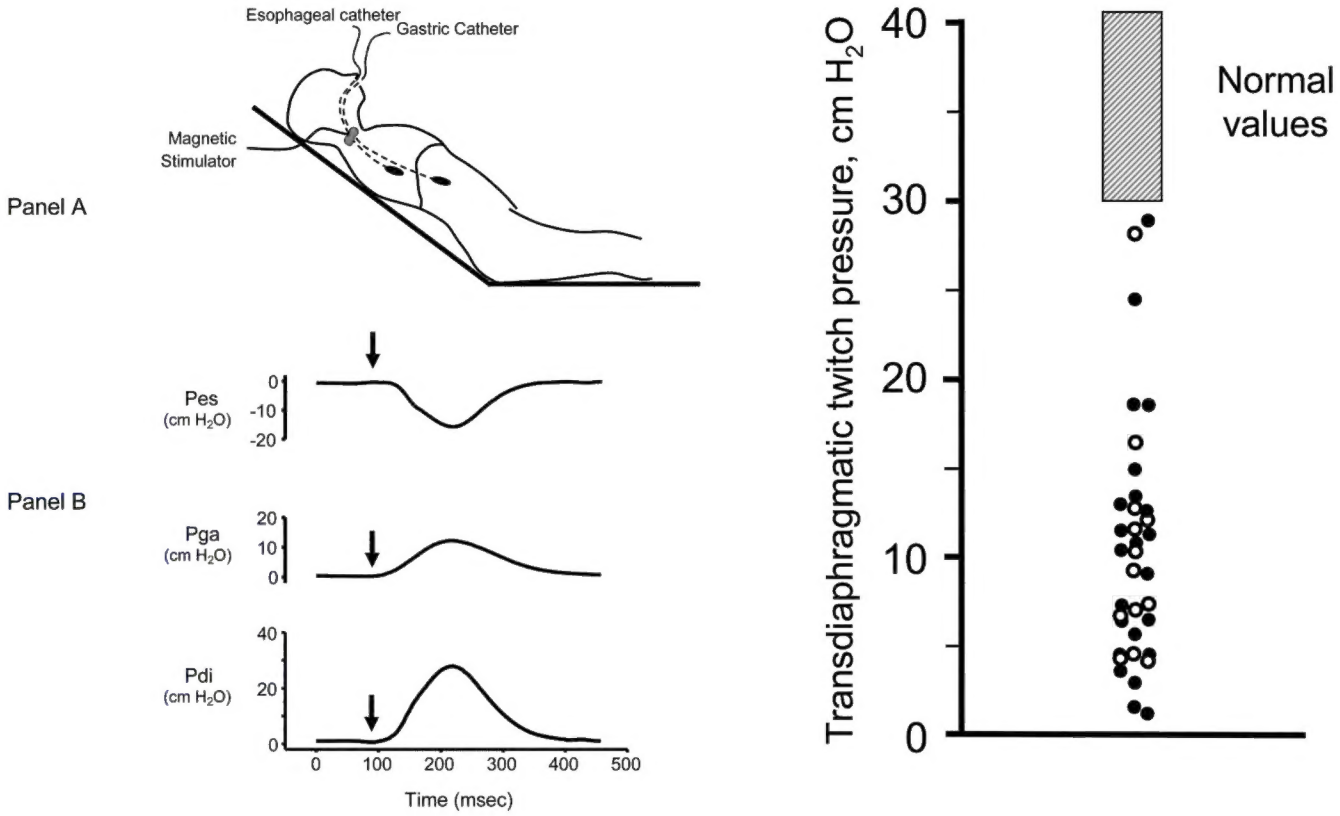

Figure 1.

The *upper-left panel* shows the instrumentation for measurement of transdiaphragmatic pressure is response to stimulation of the phrenic nerves. Balloon catheters are passed through the nose to record esophageal pressure (Pes) and gastric pressure (Pga); transdiaphragmatic pressure (Pdi) is calculated by subtracting Pes from Pga. A special magnet is used to stimulate the phrenic nerves. The *bottom-left panel* shows the fall in Pes and rise in Pga and Pdi in response to phrenic-nerve stimulation (indicated by arrows). The *right panel* shows values of transdiaphragmatic pressure in response to stimulation of the phrenic nerves in patients requiring mechanical ventilation. The boxed area represents the 95% confidence interval of values obtained in healthy subjects. Data represented by open and closed symbols are taken respectively from Cattapan et al (29) and Watson et al (30).

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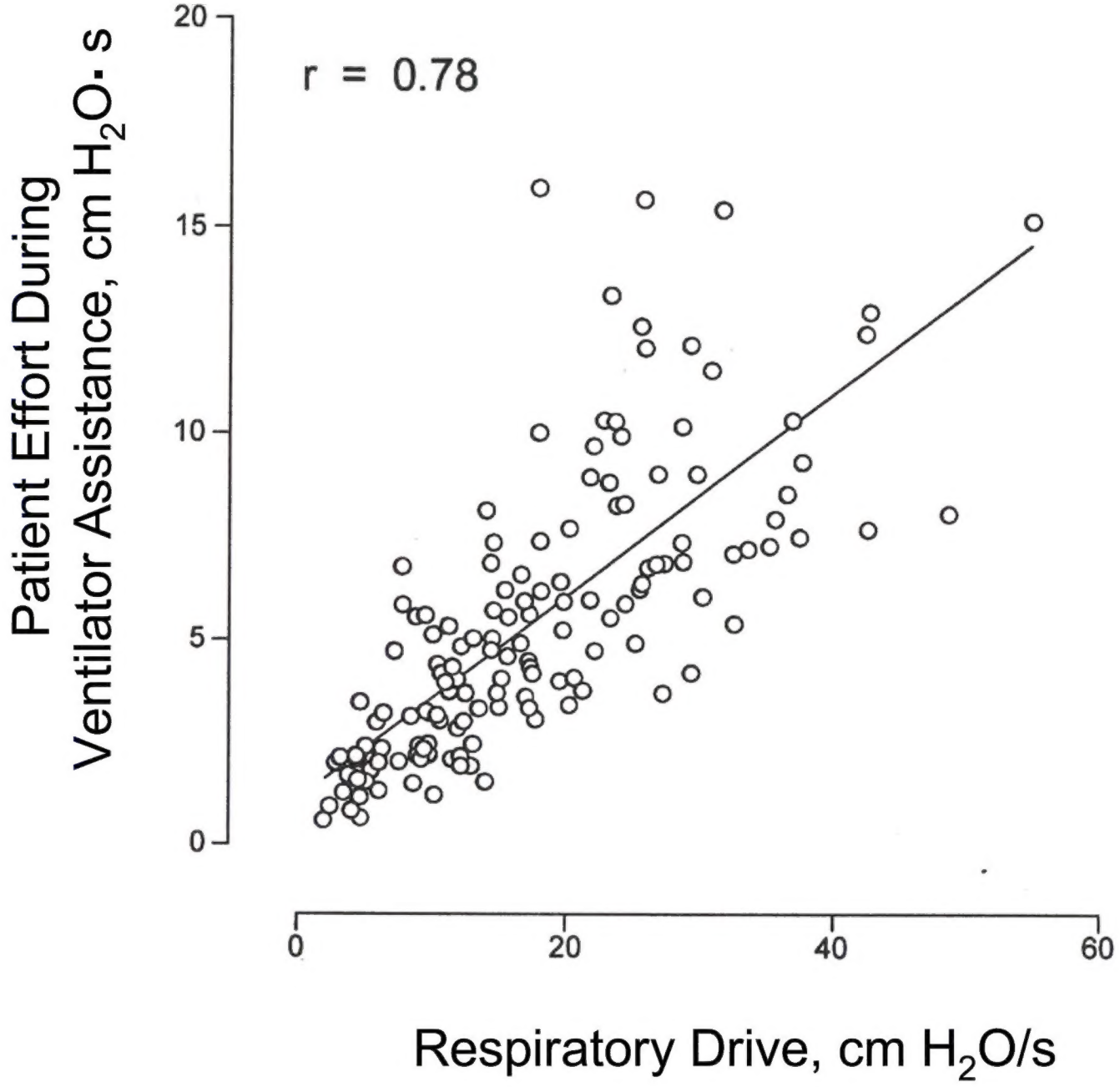

Figure 2.

Patient effort during the time that the ventilator is delivering a breath (measured as inspiratory pressure-time product per breath in cm H_2O.s) is closely related to a patient's respiratory drive (measured as dP/dt in cm H_2O/sec) at the moment that a patient triggers the ventilator (r=0.78). The inspiratory muscles of patient who has a low respiratory drive at the time of triggering the ventilator will perform very little work during the remainder of inspiration when the ventilator is providing assistance. Conversely, the inspiratory muscles of a patient who has a high respiratory drive will expend considerable effort throughout the period of inspiration even though the mechanical ventilator is providing assistance. ***(Based on data published in (***31))

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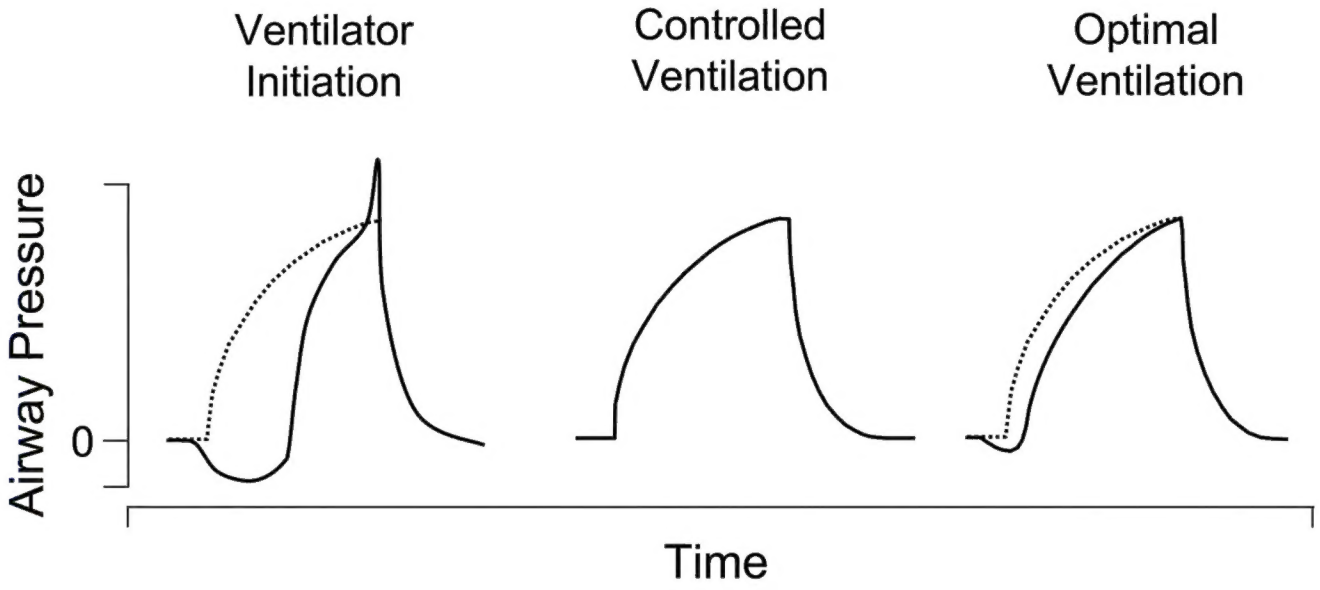

Figure 3.

Airway-pressure waveforms recorded in a patient shortly after the initiation of mechanical ventilation *(left),* in patient making no respiratory effort (controlled mechanical ventilation, *middle)*, and in a patient receiving an appropriate level of assist-control mechanical ventilation *(right).* The dashed lines on the left and right panels reproduce the tracing achieved by passive, controlled mechanical ventilation as occurs in a patient receiving neuromuscular blocking agents. The *left waveform* depicts a patient in respiratory distress who has an excessive work of breathing; this can be inferred from the initial concavity, which results from vigorous inspiratory effort, and the spike at the end of ventilator assistance, which is the result of expiratory muscle recruitment. The *middle waveform* depicts a patient making no respiratory effort and thus is at risk of developing ventilator-induced respiratory muscle weakness. The *right waveform* depicts a patient performing an appropriate amount of respiratory work: the small downward dip at the start of the breath indicates the small inspiratory effort required to trigger the ventilator, and the distance between the solid line (actual airway pressure) and dashed line (expected tracing during controlled ventilation, as in the middle panel) is proportional to the amount of work performed by the patient's inspiratory muscles while the ventilator is providing assistance. The patient in the right panel is performing much more respiratory work than the patient in the middle panel and much less work than the patient in the left panel.

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Table 1

Causes of respiratory muscle weakness

Preexisting conditions	Examples or Mechanisms
Neuromuscular disorders	Guillain-Barre syndrome
Hyperinflation	COPD
Malnutrition	Crohn's disease
Endocrine disturbances	Hypo/Hyperthyroidism
Conditions of new onset	
Ventilator-associated respiratory muscle injury	Oxidative stress/Protein catabolism
Sepsis-associated myopathy	Oxidative stress/Protein catabolism
Intensive care unit acquired paresis	Multiple organ failure
Acidosis	Decreased contractility
Electrolyte disturbances	Hypokalemia
Medications	Corticosteroids, aminoglicosides, neuromuscular blocking agents